Exploring Differences in Functional Connectivity between Senior Fallers and Non-Fallers

by

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ABSTRACT

Background: Falls among seniors are a major health issue. About 30% of community-dwelling adults aged 65 years and older experience one or more falls per year. Although not all falls lead to injury, 20% require medical attention and 5% result in fracture. Fall-related injuries are the leading cause of mortality due to unintentional injuries among those 65 and older. Key falls risk factors are categorized into physical factors (e.g. gait speed, balance, muscle strength, etc.) and neurocognitive factors (e.g. cognitive performance, brain volume, etc.). To date, few studies have examined the brain function on falls risk. My thesis explores this question through functional connectivity MRI analysis.

Method: A cross-sectional functional magnetic resonance imaging study consisted of 44 (23 non-fallers and 21 fallers) community dwelling older adults. Participants performed the finger tapping motor task and I examined for differences in functional connectivity of four age-related neural networks: default mode network (DMN), fronto-executive network (FE), fronto-parietal network (FP), and motor network (Mot).

Results: Significant between-group differences were identified in between-network functional connectivity. Fallers showed decreased connectivity between the FP network and Mot network ($p<0.05$) and increased connectivity between the FP network and DMN ($p=0.04$). No significant within-network differences were observed between the two groups.

Conclusion: Results from this study extend our current knowledge on the neural basis of falls in community-dwelling older adults, and suggest a history of falls is associated with disruptions in neural network patterns that are undetectable by traditional clinical testing. Thus, a history of falls may be an early clinical biomarker for dementia risk. Future

research is required to examine the directionality of this relationship as well as explore innovative falls-prevention strategies.

PREFACE

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1. INTRODUCTION

1.1 Falls Epidemiology and Impact

Falls are a major health care problem for seniors and health care systems. They are the third leading cause of chronic disability worldwide [1] and about 30% of community-dwelling adults aged 65 years and older experience one or more falls every year [2]. About 5% of falls result in fracture and one-third of those are hip fractures [2]. In 2004, the estimated costs for these fall-related injuries exceeded 2 billion for Canadians aged 65 years or older [3]. Other negative impact includes reduced quality of life [3], disability [3], and even death [3]. Therefore, falls prevention is a public health priority. My thesis work contributes to this public health priority by investigating neural correlates of falls risk. Gaining a better understanding of the neural basis of falls could lead to the refinement and development of behavioural, cognitive, or neuropharmological interventions for falls prevention.

1.2 Risk Factors for Falls

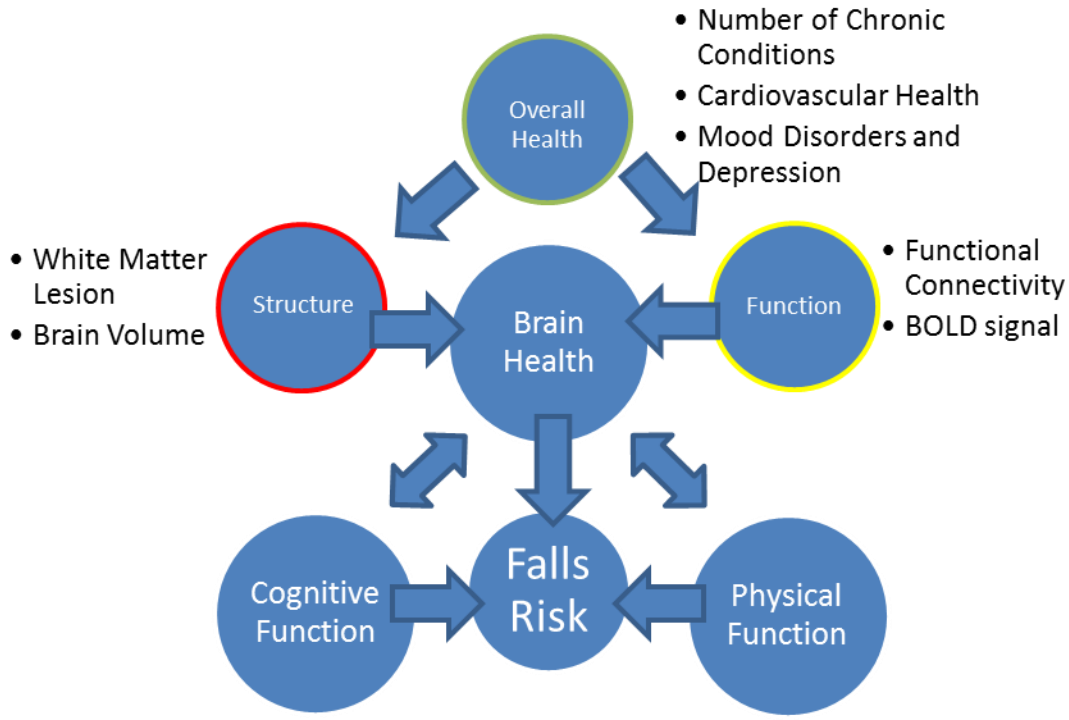
Falls are a consequence of extrinsic or intrinsic risk factors [4]. Extrinsic falls risk factors are those that can be found in the environment, such as poor footwear, icy sidewalks, and irregular stairs. In contrast, intrinsic falls risk factors are those inherent to an individual, such as weak leg strength and reduced cognitive function.

Falls risk factors can be further categorized as amendable – factors that can be changed or modified, or non-amendable – factors that cannot be changed or modified

[4]. When developing effective falls prevention strategies, the focus must be on amenable falls risk factors.

While impaired physical functions, such as weak leg strength and poor balance, are widely-recognized falls risk factors, impaired brain health may be a critical, but less examined, risk factor. I propose that the brain is a key system to investigate in the area of falls prevention because it plays a critical role in maintaining both physical and cognitive function (Figure 1). For example, the cerebellum is not only responsible for normal motor function (i.e. movement), it is also involved in executive functioning [5] (e.g., planning of movement), and hence, may represent a critical interface between mobility and cognition. Thus, damage to the cerebellum through such an event such as stroke would result in both motor and cognitive deficits, resulting in increased risk of falls. Furthermore, sub-clinical brain structural abnormalities such as white matter lesions due to small-vessel cerebrovascular disease can cause neural circuit disruptions resulting in both impaired cognitive function, specifically executive functions [6-8], and impaired balance and mobility [9-13].

Figure 1. Conceptual Framework for the Relationship Between Brain Health and Falls Risk



As indicated in Figure 1, the overall health (both physical and mental) of an individual directly impacts the brain's structural and functional integrity, which collectively impact brain health. Note that BOLD signal stands for blood-oxygen-level-dependent-signal.

For the purpose of this thesis, I conceptually define brain health as the state of this vital organ secondary to the interaction of both its structure and function. Brain health has a reciprocating relationship with both cognitive function and physical function. Specifically, brain health has a direct impact on both cognitive function and physical function. In turn, an individual's cognitive and physical function can impact brain health via lifestyle factors. For example, an individual who has intact executive functions is cognitively able

and motivated to carry out health-promoting behaviours [14] – such as dietary and lifestyle changes, including increased participation in leisure physical activity . This in turn could improve their overall brain health. Current evidence suggests that both cognitive function and physical function as key domains of falls risk in older adults. Here, we also suggest that brain health directly impacts falls risk.

Brain function is assessed by neuroimaging techniques. In recent years, significant advances have been made in both neuroimaging techniques and analysis. Such advances have greatly enhanced our ability to assess the functionality and plasticity of the brain. My thesis focuses on comparing functional connectivity between four distinct neural networks relevant to both aging and mobility between senior fallers and non-fallers.

1.2.1 Physical Function

Currently the key physical attributes identified to be significantly associated with falls risk include lower limb proprioception, visual contrast sensitivity, hand reaction time, dominant quadriceps strength, as well as balance (i.e. sway on a foam surface) and gait [2, 15, 16]. In a twelve-month prospective study, Lord et al., [15, 16] assessed each of the above risk factors. Proprioception was measured with the subject's eyes closed in an attempt to elevate the feet and match the position of the big toe with a perspex sheet in between. The differences in the position of the two toes were noted in units of degrees. Visual contrast sensitivity was tested with the standard Melbourne Edge Test, with which the subject was asked to identify the orientation of a line that is drawn through the middle of circular shapes of various contrast. The sensitivity is measured in units of decibel (dB=-10log Contrast). Reaction time was assessed in milliseconds via a simple device with light as the primary stimulus where the subjects respond to the stimulus by press of a button. Quadriceps strength was assessed by the maximum amount of extension of a spring gauge on the subject's dominant leg. Sway was tested by the amount of body displacement (in millimeters) in 30 seconds on different surfaces (firm, foam rubber) with both eyes open and closed conditions. Lord et al., [15, 16] found the combination of these five measures has a 75% predictive accuracy for falls in older people, and can determine the overall stability of an individual. The performance decline of these is associated with increase in number of falls [15, 16]. Lord and colleagues described the relative contribution (i.e. relative weighting, or how significant each item affects the overall falls risk score) for each of the items with respect to falls risk as follows: -0.33 for edge contrast sensitivity, 0.20 for joint position sense, -0.16 for

isometric quadriceps strength, 0.47 for hand reaction time, and 0.51 for postural sway on foam rubber mat with eyes open [17]. These five measures comprise the Physiological Profile Assessment (PPA). The PPA produces a falls risk score (a standardized z-score) that is a valid [15, 16, 18] and reliable [19] measure of falls risk in older adults. A PPA z-score of 0-1 indicates mild risk, 1-2 indicates moderate risk, 2-3 indicates high risk, and 3 and above indicates marked risk [20].

1.2.2 Cognitive Function

Cognitive function is broadly described as the processes including attention, working memory, problem solving, planning and strategizing, all of which are essential components in maintaining functional independence in life [21]. Cognitive impairment is an established key falls risk factor [2, 15, 16]. In a one year prospective study of 336 community dwelling seniors, Tinetti and colleagues [2] demonstrated that cognitive impairment has a negative impact on falls (relative risk = 2.3) independent of other falls risk factors such as balance and gait abnormalities, palmomental reflex and lower-extremity disability. In another one year prospective study consisted of 95 elderly persons from senior home, Lord and colleagues [15] found those individuals with cognitive impairment were more than twice as likely to experience falls (relative risk = 2.37) compared with subjects without cognitive impairment. Allan and colleagues [9] reported a prevalence of 65.7% for people with dementia to sustain at least one fall in the duration of 12 months, and the incidence ratio for falls for the subjects with dementia was significantly higher than the people without dementia (incidence risk ratio=2.55) [22].

Critically, current evidence now suggests that even mild reduction in cognitive abilities among otherwise healthy community-dwelling older adults increases falls risk [2, 23-25]. In a cross-sectional study, Liu-Ambrose and colleagues [13] showed community-dwelling women aged 65 to 75 years with probable mild cognitive impairment (MCI) - a condition with declined cognitive abilities in one or more domains of cognition while retaining intact global cognitive function and functional independence [25], had significantly higher falls risk than their non-MCI counterparts. Specifically, the presence of probable MCI was determined through the administration of the Montreal Cognitive Assessment test (MoCA) [26], and the participants completed a series standard neuropsychological tests and the PPA. The study demonstrated that those with probable MCI had significantly higher falls risk, as indicated by higher PPA scores (i.e. increased falls risk) and increased postural sway, than those without probable MCI [25].

Extending these cross-sectional results, an eight-year follow-up study by Anstey and colleagues [11] also presented evidence that increased falls risk is related to subtle cognitive decline in community-dwelling older adults [23]. Participants were assessed for cognitive function, physical and health conditions, and number of falls in the previous 12 months. Results indicated baseline performance on the Mini-Mental State Examination test (MMSE), verbal reasoning, and errors in the National Adult Reading Test (verbal ability) and declined processing speed were associated with increased rates of falling [23].

1.2.2.1 Executive Functions: A Specific Cognitive Domain Relevant to Falls

1.2.2.1.1 Key Domains of Executive Functions

Current evidence suggests that executive functions, defined as the ability to focus, to selectively attend, and to plan, are cognitive processes most relevant to falls [10, 23, 27-30]. Miyake and colleagues [17] described mental task set-shifting, working memory updating, and response inhibition as three key domains of executive functions [31] (Table 1). Specifically, set-shifting refers to one's ability to switch back and forth between various mental tasks, updating focuses on the replacement of old memory with new information, and response inhibition concerns with how to actively repress the dominant or automatic response [31]. Miyake and colleagues [17] explained that although the three domains of executive functions can be assessed individually, all three share the same underlying processes, suggesting these domains are closely linked to each other. Therefore, the performance of a complex executive functioning task requires contribution from all three aspects [31].

Specifically, my colleagues and I recently published a systematic review examining the relationship between specific cognitive processes and falls risk in older adults [30]. We examined 23 peer-reviewed articles from MEDLINE, PUBMED, and EMBASE databases with emphasis on cognitive function and falls or falls risk. Critically, we found that current evidence suggests that reduced performance on dual-tasking (performing cognitive task while completing a physical test), processing speed, set-shifting, attention, and response inhibition are consistently found to be associated with increased falls or falls risk [30].

Table 1. Executive Functions Tests and Cognitive Domains Measured

Executive Functions Tests	Key Cognitive Domains Measured	Reliability
Stroop Test*	Selective attention and response inhibition	>0.75
Trail Making Test A/B*	Set-shifting	0.64/0.79
Digit Symbol Substitution Test	Processing speed and Attention	>0.88
Verbal Fluency Test	Information processing	0.72
Digits Forward/Backward*	Working memory	>0.80

* Indicates the cognitive tests used in this study; Spreen and colleagues [32] report the Stroop Test had an averaged estimated reliability coefficient > 0.75; Trail Making Test A/B had estimated reliability coefficient of 0.64 and 0.79 respectively; Digit Symbol Substitution Test had a reliability coefficient > 0.88; Verbal Fluency Test had a reliability coefficient of 0.72; Digits Forward/Backward had a reliability coefficient > 0.80

1.2.2.1.2 Executive Functions and Aging

Executive functions decline substantially with age [33]. Importantly, even among healthy and cognitively fit (i.e. MMSE score of >27/30) seniors, a decrease in executive functions is prevalent [21, 34]. Royall and colleagues reported in a study population consisting of mostly cognitively fit members (less than 8.3% scored <24/30 on MMSE), 17.6% failed to complete an executive clock drawing task [21]. Similarly, in another prospective study investigating the effect of executive functions on functional status in normal aging, Royall and colleagues, [35] explained the MMSE is prone to underestimate cognitive impairments in the frontal system because the test does not

contain domains that specifically address executive functions. Consequently, current evidence that administered the MMSE as the primary identification tool of cognitive health may present misleading results leading to an underestimation of cognitive impairment. A nine-year observational study by Carlson and colleagues [22], indicated that for a study population of over 400 community-dwelling older women age 70 to 80 years, 49% of the study participants developed cognitive impairments over the duration of the study, with decline in executive functions as the first domain to be impaired [36].

1.2.2.1.3 Relevance to Falls

In recent years, a considerable number of studies have demonstrated the association between executive functions and falls risk [23, 24, 29, 37-39]. Liu-Ambrose and colleagues [40] propose that reduced executive functions may increase the propensity to fall via various pathways including impaired balance [41] and gait [9] secondary to reduced attentional capacity, impaired central processing and integration, and impaired execution of postural responses. Reduced executive functions may also increase falls risk via decreased judgment and diminished self-regulation [42], or indirectly increase falls risk via secondary disruptions in executive functions-related behaviour, such as a loss in motivation and initiation [43].

Specifically, multiple studies report a negative association between history of falls and reduced executive functions [28, 29, 37]. Rapport and colleagues [44] administered several standard neuropsychological tests including the Stroop Test, Letter-Number Span, and Verbal Fluency Test to assess various components of executive functions – specifically, selective attention and response inhibition, working memory, and verbal

fluency. Among the cognitive tests only the Stroop performance contributed significantly in falls prediction (p=0.036) while the combination of the discussed executive functions domains accounted for 30.3% of the variance in falls [44].

Results from other studies also suggest executive functions, as measured by these standard neuropsychological tests, are highly correlated to falls and falls risk. In a cross-sectional study, Anstey and colleagues [45] focused on three domains of executive functions and their association with falls: response inhibition – assessed by Choice Reaction Time - Location and Choice Reaction Time - Color; set-shifting – assessed by Trail Making Test; and processing speed – measured by Digit Symbol Substitution Test. They found recurrent fallers showed tendency to perform poorer on measures of processing speed as well as response inhibition [45]. In another cross-sectional study, Lord and colleagues also report study participants with history of falls performed significantly poorer on processing speed, response inhibition, and set-shifting cognitive tasks [28]. Other prospective studies also showed duplicated results that falls risks is negatively correlated with cognitive performance on set-shifting, responsive inhibition, attention, and working memory [46, 47].

Dual-task paradigm comprised of both motor and cognitive tasks is a common tool implemented in many studies to examine the relationship between cognition and motor movement as well as postural control [48-51]. For example, Holtzer and colleagues [9], in a prospective study consisted of community dwellers over the age of 70, closely inspected the association of cognition and its effects on gait speed. The study participants were assessed for their gait performances and executive functions (with various standard neuropsychological tests such as the Trail Making Test, verbal fluency

and Digit Symbol Substitution Test) then asked to recite alternating letters of the alphabet while walking on a twelve feet gait mat. The study report during dual-task condition, executive attention and working memory are significantly associated with gait speed [9]. These findings were duplicated in other studies that report poorer cognitive performance during dual-task condition is linked with increased falls risk [49, 51].

The above referenced studies clearly show executive functions are crucial for successful dual-task gait performance. Dual-task–related gait changes—for example, reduced gait speed [52]—are associated with increased falls risk [49]. Specifically, the InCHIANTI study demonstrated that poor and intermediate performance on the Trail Making Test, a standard neuropsychological test of executive functions, was associated with reduced gait speed over an obstacle course [53]. A follow-up study in this cohort also found associations between Trail Making Test performance and gait speed during various dual-task physical tests [38]. Similarly, Lundin-Olsson and colleagues [27] observed individuals unable to walk while engaged in conversation displayed a significantly less safe gait ($p<0.001$), and were able to predict falls (95% specificity) of these hospitalized older adults based on the ability to talk and walk simultaneously- an executive functioning dependent task. Likewise, Holtzer and colleagues [29] reported executive attention as measured by Trail Making B Test and Digit Symbol Substitution Test, was significantly associated with single falls (OR=0.495, $p=0.002$) as well as recurrent falls (OR=0.339, $p=0.01$). In addition, McGough and colleagues [54] proposed that gait speed and Timed-Up-and-Go (TUG) performance, important falls risk factors, were significantly correlated with the Stroop Test and the Trail Making Test ($p=0.004$

and $p<0.001$ respectively), further acknowledging the role of executive functions in falls risk among older adults.

Extending these previous studies, Nagamatsu and colleagues [55] used a virtual reality environment to examine the association between different levels of dual-task load and mobility judgements. Their hypthesis was that reduced mobility judgements under dual-task conditions are associated with increased falls risk. To achieve this, study participants were asked to cross a busy street without being hit by incoming traffic in a computer simulated virtual environment. They were instructed to only walk forward while under three conditions: no distraction (single task), music (dual-task), and phone (dual task). Nagamatsu and colleagues [55] concluded that impaired executive functions increase falls risk in older adults because this set of higher order cognitive processes play an essential role in safe navigation through the environment, as selective attention is an integral component for safe mobility. In addition, impaired executive functions appear to increase cognitive load under dual-task conditions, thereby reduce the available neural resources required to maintain proper posture, hence increase falls risk [50, 56].

In a review study, Woollacott and Shumway-Cook [50] discussed the impact of dual tasking and changes in attentional demand on postural stability of older adults. They found the level of attention required for maintaining stability varies depending on the difficulty of the additional task. Similarly, in Yogev-Seligmann and Hausdorff's [56] review article, they identified the importance of attention in gait maintenance, and they established that there is a clear relationship between executive functions (attention in particular) and gait disturbances.

Using fMRI data, Liu-Ambrose and colleagues [57] recently provided novel insight to the neural basis for the association between executive functions and falls risk. Previously they demonstrated that fallers had reduced activation in the posterior lobe of the right cerebellum during an executive-challenging cognitive task compared with age-matched non-fallers. Although the cerebellum is known for its association with motor functions, recent studies have also indicated the cerebellum's role in executive functions [58] and spatial navigation [59, 60], both of which are essential for traversing through the environment. In another fMRI study, Nagamatsu and colleagues found the regions responsible for response inhibition, such as the frontal orbital cortex, were significantly associated with changes in falls risk.

1.2.3 Brain Health and Relevance to Falls Risk

Despite the growing recognition that reduced cognitive function is a key falls risk factor, the neural basis for the association between reduced cognition and falls is unclear. Recent neuroimaging studies highlight possible neural basis for the associations between cognition and falls [6-8, 61]. These studies have largely focused on the ascertaining the significance of white matter lesion on cognitive function and falls risk [6-8].

1.2.3.1 Brain Structure

The human brain is the main component of the central nervous system. The cortex of the brain is conventionally divided into the frontal lobe, temporal lobe, parietal lobe,

occipital lobe, and the cingulated cortex [62]. Structures such as the amygdala, hippocampus, and basal ganglia are found deeper in the sub-cortical regions of the brain [62]. Functions originate from inter-regional and intra-regional communication and interaction of these various parts within the cortex. Tissues constituting the cerebral cortex are consisted of gray matter or white matter. Gray matter is comprised of neuronal cell bodies, dendrites and unmyelinated neuronal axons; while white matter is comprised of glial cells and myelinated neuronal axons [63].

Changes in white matter are commonly observed in normal aging with prevalence ranging from 50% to 98% in community dwelling older adults as reported in a review study by Xiong and colleagues [64]. Current evidence suggests white matter lesion, one form of white matter deterioration, is a manifestation of partial loss of myelin and oligodendroglial cells [64], or it can be due to cerebral small vessel arteriolosclerosis [65]. White matter hyperintensity (WMH) is a specialized term used in neuroimaging studies to describe areas of strong signals that appear on regions of white matter lesions on the structural brain images. Au and colleagues [8] reported white matter lesions are prevalent (15% in a study population of 1579) among an older population and have significant negative consequences. Specifically, individuals with white matter lesions have impaired executive functions and mobility [8]. Prins and colleagues [6] found severe white matter lesion was associated with reduced cognition. They reported increased periventricular white matter lesion negatively impacted an individual's ability to perform executive functioning tasks, particularly the Stroop Test, Digit Symbol Substitution Test, and Verbal Fluency Test (Table 1).

This can be purported by evidence suggesting white matter lesion interrupts prefrontal region of the brain and disrupt its function, leading to impaired information processing. A MRI study had critically examined the location of white matter lesions and their associated disruptions in function [66]. Participants consisted of adults aged 65 years and older with and without mild cognitive impairment (as determined by a Clinical Dementia Rating score of 0.5). These older adults underwent MRI scanning while performing a neuropsychological battery that included general knowledge, episodic memory, spatial skills, and executive functions as the cognitive domains of interest. White matter lesion was indexed by WMH volume, and through voxel-based general linear models, the regional associations between WMH and neuropsychological test scores were established. The results demonstrated lesions in the right inferior temporal-occipital white matter, left temporal-occipital periventricular white matter, and right parietal periventricular white matter were associated with reduced episodic memory. In addition, bilateral inferior frontal and prefrontal white matter lesions were linked with executive functions loss [66].

In addition to having a negative impact of cognitive function, in particular, executive functions, white matter lesions also impact an older adult's general mobility and balance. A study by Masdeu and colleagues [61] demonstrated that increased brain white matter hypodensity (a phenomenon observed in CT scans – similar to WMH found in MR images – that indicates decrease in white matter volume) was associated with reduced gait and increased balance impairment in older adults [61]. Specifically, they found older adults with a history of falls were more cognitively impaired than non-falling seniors due to white matter lesions in the brain; fallers had notably more white matter hypodensity

than non-fallers. Gait and balance are maintained and controlled by fibers ascending from the ventrolateral nucleus of the thalamus to the paracentral lobule (medial superior frontal gyrus) as well as descending corticospinal fibers [61]. White matter lesions, often found in the periventricular region, disrupt these circuits in the brain and result in motor impairment [61].

Evidence in the literature confirmed brain volume loss is observed with normal aging [67], and while the effect of the loss is widespread, its magnitude varies disproportionally across different regions of the brain [68]. Study identified the caudate, cerebellum, hippocampus as areas with greatest average loss of volume; and prefrontal and cerebellum as regions that lose white matter integrity with increase in age [68]. Studies suggest these areas are exceedingly susceptible to aging due to late maturation and therefore contain greater amount of thin myelinated fibres that are more vulnerable [69, 70]. Impaired cognition is associated with neuroanatomical deterioration particularly in the prefrontal, posterior parietal and temporal cortices [71].

Extending from previous evidence that cardiovascular exercise is associated with beneficial effects on cognitive function [72], studies report cardiovascular exercise also show positive structural changes in the brain [73, 74]. Specifically, Colcombe and colleagues conducted a randomized controlled trial comprised of community dwelling seniors [74]. They found individuals participated in the aerobic training showed significant increases in both gray and white matter volume over the six-month intervention. Regions that showed greatest increase in volume included the anterior cingulate cortex/supplementary motor area, the right inferior frontal gyrus, left superior temporal gyrus, and anterior white matter [74]. In a separate randomized controlled trial,

Weinstein and colleagues [73] inspected the association between higher cardiovascular fitness and executive functions with respect to gray matter volume. The study participants were assessed for their spatial working memory and response inhibition capacities by the Spatial Working Memory Paradigm and the Stroop Test respectively. The results show increased cardiovascular fitness level is associated with higher gray matter volume across the entire brain, including the dorsolateral prefrontal cortex, a region known to be highly susceptible to aging [67]. Furthermore, Weinstein and colleagues [73] demonstrated specifically regions in the right inferior frontal gyrus and precentral gyrus mediated the association between fitness and Stroop Test performance; while regions in the middle frontal gyrus and precentral gyrus mediated the association between fitness and spatial working memory performance. Both mediations contribute to the conclusion that higher fitness is related to greater gray matter volume and improved cognitive performances [73].

1.2.3.2 Brain Function and Plasticity

While the results of these neuroimaging studies contribute to our appreciation of the importance of brain structure to falls risk, they do not provide specific guidance for refining or developing falls prevention or rehabilitation strategies because white matter lesions are not modifiable once they present – at least based on current available evidence [57]. In contrast, brain function can be altered beneficially [75-78] – even among seniors [75, 77] and after stroke [79, 80]. In a review study, Hodics and colleagues [79] selected and reviewed clinical neuroimaging studies of stroke patients that underwent physical training as the primary method of rehabilitation. Despite variation in the size and location of the lesion, they found that the majority of the studies

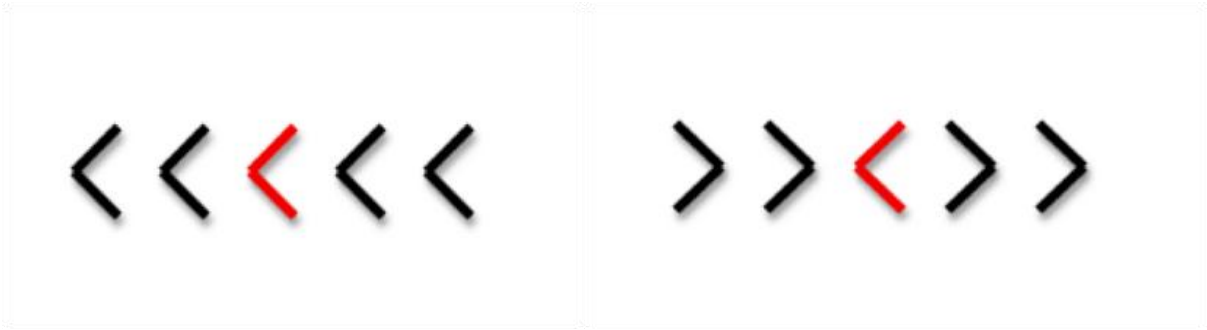
report motor rehabilitation can improve the motor functional status of the subjects by increasing activation of the motor network (Mot; i.e. primary motor cortex, premotor cortex, supplementary motor area) in the same hemisphere of the lesion [79].

A fMRI study looking at the effects of aerobic training on neural plasticity and cognitive function demonstrated fitter, healthy older adults were able to perform executive functioning task and faster and with higher efficiency in resolving conflicting stimulus as well as show greater levels of activation in attentional-control regions in the brain (middle frontal gyrus, superior frontal gyrus, superior parietal lobule) and reduced activation in the anterior cingulate cortex [75]. Possible explanation for this effect is described in part by studies using animal models, which have shown fitness training increases vascularization of the motor cortex, and higher vascularization leads to greater reserve capacity to respond in conditions that requires higher oxygen expenditure. Also, in rodent studies aerobic training was reported to increase the level of neurotrophin factor, thereby improve cell proliferation, prolong cell survival, and induce neurogenesis in the hippocampus, hence improving spatial learning [75]. Nevertheless, it is difficult to assess how accurately these results from animal studies correspond to the findings from Colcombe's research on humans; especially when their studies placed more emphasis on executive functions (i.e. prefrontal lobe) and not the motor cortex.

Furthermore, in a recent functional MRI study, Liu-Ambrose and colleagues showed resistance training can modify brain activity level during the flanker task (Fig. 2), a measure of selective attention and response inhibition. Specifically, they showed functional plasticity in the areas of the frontal orbital cortex and temporal gyrus [81].

Figure 2. Flanker Task Paradigm

a) Congruent **b) Incongruent**



1.3 FMRI and Functional Connectivity: A Specific Focus of this Thesis

Functional magnetic resonance imaging is a neuroimaging technique that detects neuronal activation via changes in the blood-oxygen-level-dependent signals (BOLD). BOLD signals are indicative of the amount of neural activity in the brain; specifically, this information is derived from the concentration of oxy-haemoglobin found in the arterioles of the brain. Stronger signal is acquired from a higher level of oxy-haemoglobin, reflecting an increased neuronal activity. With this information, I can create activation maps that describe the average engagement of brain regions during specific condition (i.e. rest or task) in response to particular stimuli. Here I must distinguish brain activation maps from model-statistic maps. Brain activation maps display the regions activated (as a result of the introduced stimulus) on a high resolution structural image

and is used to infer the relationship of evoked activation – the association between different active voxels (or inactive voxels) in the brain; whereas model-statistic maps shows the magnitude of activation found in different brain regions with respect to cognitive state under study. Through brain activation maps, I can observe the interaction of different neural networks and how these systems work together to achieve various cognitive function. Functional connectivity is defined by this integration of different interacting brain regions activated in sync to perform different tasks.

The most widely accepted definition of functional connectivity is the temporal correlation between spatially remote neurophysiological events [82]. In other words, if physically distant brain regions demonstrated synchronized patterns of activity, they are considered functionally connected [83]. Modern cognitive neuroscience suggests the existence of large scale neural networks within the brain, consisting of different brain regions, that are involved in different components of cognition, such as executive functions and motor-planning [83].

The traditional view of neuroanatomical connectivity states that the balance between anatomy and function is maintained by constant formation and elimination of physical connections [84]. The more functionally utilized axons (more active) have competitive edge over the less used ones, which may eventually be replaced [84]. A major drawback of this concept is that cortical reorganization is a process that may be too slow to explain many of the higher order cognitive functions. Instead, functional connectivity would be a better mechanism for explaining this phenomenon [84]. A key benefit of studying functional connectivity is that it allows us to derive effective connectivity between regions of the brain if the appropriate model is applied to establish

causal relationships [84], considering functional correlations are sometimes constrained by anatomical connectivity (for example, disrupting the commissural fibre was found to reduce between-hemisphere functional connectivity) [85]. Hence functional connectivity is a technique that supplements what the traditional study has demonstrated, and is a useful tool to identify and understand the functional neural basis for falls among older adults.

1.3.1 Methods to Study Functional Connectivity

Similar to other fMRI studies, functional connectivity can be investigated under task-evoked conditions. Task-evoked variance can be introduced via block design or event-related paradigms. Generally speaking, block design is ideal for activation detection due to the clustering of responses with short intervals. It is used to measure variations in the average signal level between different steady states. Because this method measures the mean signal level, it assumes that the functional connectivity is constant over time for the duration of the condition. Functional connectivity of different regions can be accurately determined by extracting time-series data of a particular condition at various time point and merging these individual volumes as one continuous timecourse that indicate a single condition. On the other hand, event-related design is used to estimate the shape of hemodynamic response function and measure temporary fluctuation in the signal produced by a disturbed baseline steady state [86]. Because of the long duration between trials, it is difficult to infer functional connectivity through the signal itself. In this case, relationship between the voxels that were involved in the signal fluctuation must be evaluated with beta-series correlation. Beta-series correlation analysis produces a set of beta-parameter estimates for any voxel in the brain that

reflect how much activity within that voxel is attributed to different stages of a task (cue, delay, etc.) [87]. In other words, instead of finding correlations between signals from each voxel, this method generates beta-parameter estimates then establishes functional connectivity by finding correlation between these parameter estimates.

Different from traditional fMRI studies, functional connectivity can also be examined without an external stimulus (i.e. no task required). This is a unique way of examining brain function that has recently captured the interest of many researchers, and is referred to as resting state analysis. The characterization of functional connectivity of the resting state networks can be achieved through two ways: 1) independent component (ICA), and 2) the region of interest (ROI) analyses [88]. Independent component analysis offers a way to detect multiple resting state networks at once, and the voxel value is reflective of how well the time series data of a particular voxel is correlated with the mean time series of a specific resting state network. Region of interest analysis requires a predetermined set of a-priori regions that can be used to correlate with other locations in the brain. The voxel values in ROI analysis reflect the correlation between the voxel and the designated ROI. For the purpose of this thesis, I only considered ROI analysis.

Not restricted by the scanning technology, functional connectivity can and has been studied with electroencephalogram (EEG) as Toma and colleagues [89] had accomplished in their study. This imaging technique offers measurement of neuronal activity with high temporal resolution (milliseconds) at the expense of spatial clarity (>1 mm) [89]. Similarly, Brooke and colleagues recently showed functional connectivity can be measured through magnetoencephalography (MEG) [90]. They provided evidence

that MEG is capable of acquiring comparable spatial resolution to MRI under particular circumstances and, in conjunction with MRI, can generate results demonstrating the underlying electrodynamic mechanisms of connectivity.

1.3.2 Functional Connectivity and Aging

This section provides an overview of neural systems particularly relevant to the effects of aging that were examined in this thesis.

1.3.2.1 Resting State and the Default Mode Network

Resting state network functional connectivity is a powerful tool for studying changes in brain function in clinical populations including Alzheimer's disease, autism, and schizophrenia [88]. Studies report variations in resting state functional connectivity can be used to distinguish patients with Alzheimer's disease, depression, mild cognitive impairment, and schizophrenia from healthy individuals [91-93]. This relatively novel technique serves as an alternative to traditional fMRI that can sometimes be constrained by the functioning status of the study participants (i.e. often only the higher functional individuals can successfully complete the required cognitive tasks). The default mode network (DMN; a network found within the resting state networks), specifically, it is highly relevant in the early course of Alzheimer's disease development, schizophrenia, as well as mild cognitive decline due to aging [93-96]. Before proceeding to discuss the details of the DMN, we need to understand the basis of seed-voxel based functional connectivity measurement - the primary analysis technique of the thesis.

Seed-voxel analysis is a method to map whole-brain connectivity by using correlations derived from the BOLD signal data. Critically, the analysis produces Pearson's correlation coefficient identifying which brain regions are active in the same instance and thereby indicating brain regions of high and low functional connectivity with respect to the seed. Specific to seed-voxel analysis, preprocessing commonly included the removal of nuisances from the cerebral spinal fluid, white matter, and global signals. Functional connectivity between brain regions is established by seed-voxel analysis without making the distinction that whether or not these regions are intrinsically related (i.e. from the same network). In other words, this analysis method is used to reveal correlation between different voxels in the brain without consideration of their association to functional networks [97]. Essentially, seed-voxel connectivity compares voxels between specified regions to see if they are correlated and disregard all intrinsic interactions that might be present at these regions, hence ignoring the possibility that the regions in comparison might be of the same functional network.

Changes in the BOLD signal time series data are the basis to assess functional connectivity in MRI. These variations in the data can be attributed to three sources: 1) inter-subject variance, 2) task-evoked variance, and 3) intrinsic variance. Intrinsic variance is understood as spontaneous fluctuations in hemodynamic response without the presence of a stimulus. Researchers found these synchronous changes in BOLD signals in subjects during rest to be a function of underlying neuronal activity and can be used as markers for functional connectivity [98]. Because this effect is often observe while subject is at rest, it is referred to as the "resting-state" functional connectivity, and the associated networks are thereby known as the "resting-state networks" [99].

Therefore, I can apply resting-state functional connectivity analysis to any neural system and the networks that are present during rest condition can be designated as part of the resting-state networks. The DMN is an example of a resting-state network because it had been reported to show correlated signal fluctuations at rest [99]. In addition, another study demonstrated that under resting condition, the medial superior frontal cortex is positively correlated with the primary motor, postcentral and paracentral cortices, insula, superior/middle temporal cortices, and the dorsal anterior cingulate cortex [100]. Similarly, posterior cerebellum was also found to exhibit resting state between-network functional connectivity with the prefrontal cortex [101].

The DMN contains multiple brain regions (e.g. middle prefrontal cortex, posterior cingulate) essential for cognitive processes such as memory and executive functions [102, 103]. A study conducted by Damoiseaux and colleagues [104] showed aging negatively impacts the functional connectivity of intrinsic brain activity within the DMN. Fox and colleagues [105] suggested that even without the presence of an external stimulus (i.e. brain is at rest), various components of the brain remain active, such as the motor cortex, visual cortex, as well as the dorsal and ventral attention network [106]. In Damoiseaux's study [104], a battery of neuropsychological test was assessed, from more global cognitive assessment such as MMSE and New Adult Reading test, to more domain specific measurements including Digits Forward/Backward Test, Wechsler Adult Intelligence Scale Symbol Substitution – encoding (a component of the test), Stroop Test, Trail Making A, 15-word test, visual association test, WAIS symbol substitution – memory (a component of the test), Memory impairment screen plus (these target memory), Wechsler Intelligence Scale for Children maze, Fluency, and Trail Making B

Test. The authors found a direct relationship between aging and loss of connectivity in regions within the DMN, and this decreased functional connectivity within the network was associated with reduced performance of the Trail Making B Test, which suggested executive functions decline. This evidence coincided with Andrews-Hanna's finding in their study that investigated age-related neural system disruption [103]. Andrews-Hanna and colleagues [103] identified lateral parietal cortex, hippocampal formation, parahippocampal cortex and most importantly, posterior cingulate cortex/retrosplenial cortex as regions within the DMN that were most impacted by aging. These areas were highly correlated with memory (r=0.41), processing speed (r=0.40), and executive functions (r=0.35). Additional confirmation was provided by Madden and colleagues [107], who conducted a study that also found age-related changes while performing executive functioning task. Specifically, the study by Madden and colleagues [107] reported a significant difference in mean functional connectivity of cue preparatory processes-related brain regions (the fronto-parietal (FP) network) between older and young adults. The authors demonstrated a negative correlation between increased connectivity and faster reaction time (i.e. better performance).

Despite the fact that they used a different scanning technique, Stam and colleagues [108, 109] found similar association between cognitive decline and disrupted functional connectivity. The researchers studied functional disconnection of the brain of patients with Alzheimer's disease using magnetoencephalography (MEG) neuroimaging technique. MEG records magnetic signals created by naturally occurring electrical currents in the brain, and outputs the recorded data in the form of frequencies. Various frequency bands would reflect different brain function, for example, the alpha band is

associated with attention and semantic memory, whereas the gamma band is associated with perception [108]. Functional disconnection in MEG then refers to a decreased synchronization in multiple frequency bands, resulting in disruption in multiple brain function. In another study, they reported that people with dementia display a significant reduction in functional connectivity in the left fronto-parietal, fronto-temporal, parieto-occipital, and temporo-occipital lobes [109].

1.3.2.2 Executive Network and Motor Network

Evidence suggests there are age-related differences in brain activation while performing executive functioning tasks. Particularly, DiGirolamo and colleagues [110] and Gold and colleagues [111] both found increased activation in the FP network associated with dual task processing in older adults compared to younger adults. Given that older adults demonstrated different activity patterns during executive functioning tasks, the older population might exhibit a difference in functional connectivity of activated brain regions compared with younger population (different activity patterns may be due to different synchronous activity in regions of the brain). Madden and colleagues [107] compared the functional connectivity of younger and older adults associated with performing a task-switching paradigm (each trial required the participant to provide a decision on categorizing a presented cue word – large/small or manmade/natural while the categorization of the stimulus is randomly selected across block – i.e. can be repeated or switched) and reported a lower average correlation of event-related activation (i.e. less functional connectivity) for older adults. In addition, Madden [107] demonstrated that during the switch trials, extensive cortical activation was observed – in the right prefrontal and occipitoparietal regions as well as the left cerebellar area – without

significant differences between age groups. This suggests age-associated decline in cognitive function of cue related preparatory processes is not detectable through activation-based analysis but is observable only with functional connectivity methods.

Researchers of a recent functional imaging study examining the effects of aging on the functional architecture of the Mot network in the brain reported that aging is associated with changes in the functional connectivity [112]. On whole brain activation maps, Marchand and colleagues [112] showed there was an increased activation of the anterior cingulate cortex, frontal cortex, and precuneus for the older adult group compared to the young group. With functional connectivity analysis, they reported there was an increased connectivity between the primary motor cortex and the primary somatosensory cortex within the older adult population. They found that greater connectivity strength is driven by a stronger cortical connectivity with the ventral anterior nuclei of the thalamus and the caudate. This enhanced cortical connection was associated with reduced cognitive performance (i.e. higher number of errors in the Push-Turn-Tap performance – a task that assessed motor-planning, motor-speed, and motor-learning abilities. Participants responded to a visual cue with complex movement patterns on joystick and button-press.), and directly contributed to reduced motor functioning (i.e. motor-planning) [112]. Critically, age explained 44% of the variance in Push-Turn-Tap performance while functional connectivity accounts for an additional 8.5% [112]. This confirmed the authors' hypothesis that changes in functional connectivity of the brain were reflective of decrease in brain function [112]. Furthermore, changes in functional connectivity were independently associated with cognitive performance.

1.3.3 The Motor Task

The finger tapping test is recognized as a key measure for identifying neuropsychiatric disorders, neurological illnesses and movement disorders [113]. Particularly, in women, the task was demonstrated to be highly sensitive in differentiating Alzheimer's disease from other dementia [114].

In fMRI studies, the finger tapping motor task has been shown to elicit large BOLD signal changes in the resting-state Mot network [115]. Specifically, the experimenters used a block design motor task in which the participants were presented with three blocks of 60 second long (each block) test. The subjects were asked to respond to auditory cue (a continuous beeping) by finger tapping [115]. The regions of interest were selected via whole-brain mapping – large regions drawn around predetermined landmarks -- and only areas activated during task were included. The authors established functional connectivity by calculating partial correlation coefficient for these regions of interest. A notable change in the motor cortex is observed even with the movement of a single finger, and one study demonstrated increased complexity in finger tapping pattern induced a greater signal change in the primary motor, supplementary motor, cerebellum, thalamus, and basal ganglia regions [116]. For this particular study, the researchers applied a block design task consisted of three components – a 500 second rest, a 500s finger tapping with visual cue (interjected with periodic rest), and 25 cycles of serial-17 subtraction from a random three-digit number [116].

Another study found the rate of finger movement is associated with functional coupling of brain regions [89]. Specifically, they showed faster finger tapping is correlated with continuous functional coupling between motor cortical regions [89]. The authors administered a block design paradigm that involved repeated thumb abduction at various rates (0.5, 0.75, 1, 2, 3, 4 Hz) based on an auditory tone. Functional data was acquired via electroencephalogram, and electrodes placed on regions of interest – left and right sensorimotor areas as well as the medial frontal area. By obtaining event-related correlation, the researchers were able to determine functional coupling of the motor regions with respect to different movement speed.

Newton et al., [115] explained this increase in correlation is a consequence of the recruitment of additional voxels rather than variations within particular sets of voxels. Most importantly, they reported the primary motor cortex is highly correlated with the supplementary motor area at all times; while cerebellum is functionally connected with the primary motor cortex only during finger movement [115].

1.3.4 Research Question and Hypothesis

Given the intrinsic relationship between brain health and mobility/falls (see Figure 1), I hypothesize that there are differences in functional connectivity between senior fallers and non-fallers. Previous studies have suggested the impact of aging on the DMN, and how regions (i.e. posterior cingulate cortex/retrosplenial cortex) within this neural system are closely related to executive functions [102-104]. Furthermore, dorsolateral prefrontal cortex was also significantly involved in the maintenance of standing balance

[117]. Thus, I hypothesized for senior fallers to show less within network functional connectivity than non-faller older adults, particularly the frontal and temporal regions of the FP network, DMN and fronto-executive (FE) network. Secondly, evidence showed faster finger movement is associated with greater functional coupling of the Mot network [89], therefore, I expect to observe greater Mot network connectivity (M1, supplementary, and cerebellum) in non-fallers during the motor-phase of the finger-tapping task since non-fallers (with better motor coordination) are capable of registering higher number of button-press (thereby more finger movement) than fallers. Lastly, I expect to find reduced connectivity in most regions within the DMN in fallers as literature suggests aged brain is reported to show reduced within-network connectivity in the DMN [88]. In terms of between network connectivity, Voss and colleagues [118] reported aging is associated with increased connectivity between the DMN, FE network, and FP network due to the inability to differentiate neural networks (decreased specificity) for compensatory brain activity. Thus, I expect to see increased functional connectivity between the DMN, FE and FP networks in the fallers under the assumption that because fallers showed more cognitive impairments, their neural system should resemble a more aged brain (i.e. advanced aging).

Intrinsically, falls are influenced by physical and cognitive risk factors (Figure 1). It is important to study executive function as well as also understand the functional connections between different neural networks. This provides deeper understanding of the underlying neural basis for falls as well as supplements the current evidence on complex cognitive functions associated with falls risk. Therefore to extend previous works on brain function and falls risk, a cross-sectional comparison study was

conducted to examine the differences in ***functional connectivity*** of the DMN, FE network, FP network and the Mot network between community-dwelling senior fallers and non-fallers.

2. METHODS

2.1 Study Design

This cross-sectional study included community dwelling adults aged 70 to 80 years. Because age is broadly accepted as a key risk factor for falls and cognitive impairment, it is one of the key important eligibility criteria for the study, whereas ethnicity or gender was not restricted.

2.2 Inclusion Criteria

1. Aged 70 to 80 years;
2. Understands, speaks, and reads English proficiently;
3. Right hand dominant (as determined by the Edinburgh Handedness Inventory [119]) as hand dominance influences neural activity as assessed by fMRI [120];
4. Able to walk 6 meters independently;
5. Visual acuity of at least 20/40, with or without corrective lenses; and
6. Able to provide informed consent.

2.2.1 Specific Inclusion Criterion for Recurrent Fallers: An individual must have experienced $\geq$ two minimal displacement non-syncopal falls in the previous 12 months. Falls is defined as "*unintentionally coming to the ground or some lower level other than as a consequence of sustaining a violent blow, loss of consciousness, sudden onset of paralysis as in stroke or an epileptic seizure*" [121].

2.2.2 Specific Inclusion Criterion for Non-Fallers: An individual must not have experienced greater than one minimal displacement falls (with or without syncope) in the previous 12 months. This was determined based on three sources: 1) participant recall; 2) participant's immediate family member recall; and 3) participant's physician.

2.2.3 Matching of Recurrent Fallers and Non-Fallers: To control for the number of possible confounding variables in the association between executive functioning and a recent history of falls, I frequency matched recurrent fallers and non-fallers by sex (i.e. male and female).

2.3 Exclusion Criteria

1. Diagnosed with a neurodegenerative disease (e.g., Parkinson's disease);
2. Diagnosed with a psychiatric condition (e.g., depression);
3. Diagnosed with dementia (of any type) or cognitive impairment;
4. Had a stroke;
5. Have clinically significant peripheral neuropathy or severe musculoskeletal or joint disease;
6. Taking psychotropic medication or cholinesterase inhibitors;
7. Have a history indicative of carotid sinus sensitivity (i.e. syncopal falls);
8. Resides in a nursing home, extended care unit, or assisted-care facility;
9. Does not meet the specific scanning requirements of the UBC MRI Research Centre. I excluded anyone with: pacemaker, brain aneurysm clip, cochlear implant, recent surgery or tattoos within the past 6 weeks, electrical stimulator for nerves or bones,

implanted infusion pump, history of any eye injury involving metal fragments, artificial heart valve, orthopedic hardware, other metallic prostheses, coil, catheter or filter in any blood vessel, ear or eye implant, bullets, or other metallic fragments.

2.4 Recruitment of Fallers and Non-fallers

Both fallers and non-fallers were recruited from communities within the metropolitan Vancouver. Primarily, the recruitment strategy was completed through advertisement postings on local newspaper. The interested participants then contacted the research coordinator, Alison Chan, who provided detailed information regarding the study as well as conducted the initial screening for eligibility. The goal was to recruit 20 senior fallers and 20 non-fallers with this recruitment strategy.

2.5 Measurement

All the eligible participants were scheduled for two assessments after screening – a clinical assessment and an MRI and fMRI assessment. Clinical assessments were held at the Center for Hip Health and Mobility (100 minutes). Functional MRI assessments were completed at the UBC High Field MRI Center at the UBC Hospital (90 minutes). Though temporal proximity between the two sessions is ideal, it is often not feasible due to the availability of the MRI. From experience, the average time to acquire MRI access is three weeks; therefore, allowed a maximum time lag of four weeks between the clinical assessment and the fMRI session.

Screening: The screening session duration was 15 minutes, and three tests were used to examine eligibility.

1. Cognitive Function**:** Global cognitive function was assessed using the MoCA (37); MoCA scores below 26/30 are indicative of mild cognitive impairment. *(Completion Time: five minutes)*
2. Depression**:** Depression may influence performance on neuropsychological tests and has been identified in the prodromal stage and as a risk factor for developing Alzheimer's disease [122]. The General Depression Scale was administered; it screens for depression by self-report statements. A score $\geq$ four indicates possible depression. *(Completion Time: five minutes)*
3. Edinburgh Handedness Inventory: Handedness was assessed by the Edinburgh Handedness Inventory [119] that asks participants to indicate which hand they would use in ten different activities. Scores range from 100 to -100 with 100 indicating right hand preference for all ten activities. *(Completion Time: five minutes)*

2.6 Clinical Assessment

This session took 85 minutes and included measurement for: 1) general descriptors (50 minutes) and 2) relevant covariates (35 minutes). The order of the tests is as listed here.

2.6.1 Descriptors

1. Anthropometry: Measured standing height to 0.1 cm. Weight was measured to 0.1 kg. *(Completion Time: five minutes)*
2. Falls History, and Socioeconomic Status: Falls history in the last twelve months [123], and socioeconomic status was ascertained by questionnaires administered by a trained research assistant*. (Completion Time: 15 minutes)*
3. Executive Functions: Assessed: 1) set shifting using the Trail Making Test A and B (performance calculated by B-A) [32]; and 2) working memory using the verbal Digits Forward and Backward Test (performance calculated by Forward – Backward) [124]. And 3) response inhibition using the Stroop Test (performance calculated by Stroop 3-2) [81]. The Trail Making Test A and B requires the participant to manually connect numbers and letters in consecutive (Part A; one to two to three, etc.) and alternating order (Part B; i.e. start at one going towards A then two to B, etc.). Verbal Digits Forward and Backward Test require the participant to verbally recite a set of previously instructed numbers in order (forward and reversed order respectively). Stroop Test requires the participant to verbally state the printed color of a word presented independently of the color name of the word (i.e. the word “blue” printed in red color should be responded as “red”). *(Completion Time: 20 minutes)*
4. Balance and Mobility: Balance and mobility was measured using the Short Physical Performance Scale [125]. For this Scale, participants were asked to perform standing balance, walking, and sit-to-stand. Each section was given a score out of four points, which sum up to a total of 12 points. Older adults with score less than six points were reported to be more at risk of developing mobility-related problems

(relative risk=4.9) [125]. TUG test was also administered to measure balance and mobility in older adults [126]. For this test, participants were assessed by the completion time: 14 seconds or less for healthy older adults; 20 seconds for older adults that might require assistance; and 30 seconds or more for frail older adults [126]. *(Completion Time: 10 minutes)*

2.6.2 Relevant Covariates

Impaired physiological function and physical inactivity are associated with falls [127, 128] and reduced cognitive performance [129, 130]. In addition, fitness level is positively correlated with the brain's attentional and response inhibition network [75]. These are the potential confounders that were accounted for during data analysis. The assessments for these covariates are listed here, and the order of the tests is the same for all participants.

1. Physiological Falls Risk: Each participant's physiological falls risk profile was assessed using the short form of the Physiological Profile Assessment (PPA)© [20] (Prince of Wales Research Institute, Sydney, Australia; www.powmri.unsw.edu.au/FBRG/FBRGhome.htm). The short form PPA is a set of five tests: 1) visual contrast sensitivity: requires the participant to indicate the direction of the midline of differently shaded circles – this assesses depth perception; 2) lower limb proprioception: requires the participant to lift feet, with eyes closed, and match the position of both big toes separated by a perspex sheet; 3) dominant quadriceps strength: requires the participant to extend a spring gauge attached to the dominant leg; 4) hand reaction time: requires the participant to press a button

when a light is flashed on the device; 5) sway: requires the participant to maintain balance with eyes open and closed on a foam pad. (*Completion Time: 15 minutes)*

2. Activities-Specific Balance Confidence Scale (ABC): The Activities-Specific Balance Confidence Scale, a 16-item scale that assesses falls-related self-efficacy [131] and a documented predictor of falls [132], was ascertained by questionnaire administered by a trained research assistant*. (Completion Time: five minutes)*
3. Functional Comorbidity Index: The Functional Comorbidity Index is a 21-item list of diagnoses that calculates the total amount of comorbidities of an individual and is used to estimate the association of comorbidity and physical function [133]. This questionnaire was administered by a trained research assistant*. (Completion Time: five minutes)*
4. Physical Fitness: Assessed physical fitness by the 6-Minute Walk Test (6-MWT) [134] -- a walking test of cardiovascular capacity in older adults [135]. The participant was timed for six minutes and the total distance walked was recorded. Also assessed the maximum oxygen uptake (VO_2) as measured by a portable metabolic measurement system during the 6-MWT and entered it a covariate in the models. Kervio and coworkers [134] demonstrated that in healthy older adults, the 6-MWT represents a sub-maximal exercise, but at almost 80% of the VO_2 (max). *(Completion Time: 10 minutes)*

2.7 Functional MRI

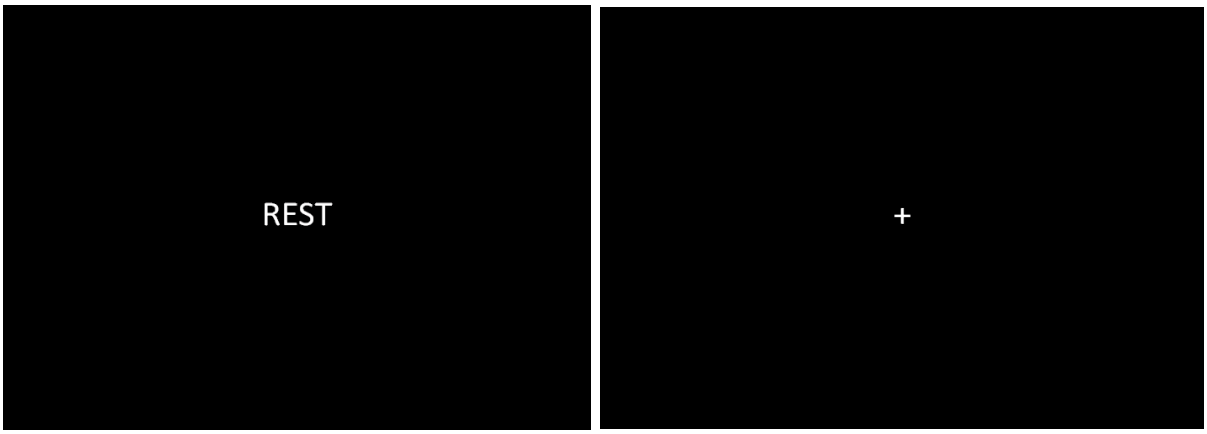
The fMRI session duration was 90 minutes. Functional magnetic resonance imaging specifically examines the blood-oxygen-level-dependent signal in the brain. This imaging technology is capable of acquiring time-series of the BOLD signals, and this information is used to make an accurate inference to region-specific neural activity while a task is performed by the participant. The UBC High Field MRI Center at the UBC Hospital provides access to a 3.0T Intera Achieva MRI scanner (Phillips Medical Systems Canada, Markham, Ontario), and all fMRI data was collected through this machine. Because this study is explicitly targeting neural activations, only brain scans was acquired via an 8-channel SENSE neurovascular coil (Phillips Medical Systems Canada, Markham, Ontario) placed around the head of the participant. The functional imaging parameters were: repetition time (TR) of 2000 milliseconds (ms), echo time (TE) of 30 ms, flip angle (FA) of 90 degrees, field of view (FoV) of 240 mm, acquisition matrix 80x80, 166 dynamics, voxel size and slice thickness of 3 mm. The high resolution T1 structural images were acquired with the following parameters: TR of 7.7 ms, TE of 3.6 ms, 170 slices, FA of 8 degrees, FoV of 256 mm, acquisition matrix of 256x200, voxel size and slice thickness of 1 mm.

During scanning, participants were requested to perform a task designed to assess brain functionality while performing a test that is intended to increase cognitive load in the motor system. The task itself serves 3 functions: 1) it is designed to elicit brain activation in the left and right motor cortex; 2) it enables us to observe the amplitude of activation for task and rest conditions; and 3) it is also a tool to study brain functional connectivity (e.g. DMN). The DMN is a network of different brain regions that increases

activity when the brain is at rest [136]. During the scan, the participant was shown a command followed by a series of pulsing “+” sign. The “+” sign pulses at a constant rate and the participant’s task is to tap buttons in sequence from index finger to middle finger to ring finger and lastly little finger in accordance to the pulse. The command indicates which hand to use (e.g. Left or Right) or rest when “Rest” is shown. The time series data collected was recorded and used for analysis. (Figure 3)

Figure 3. Motor task

a) Command Cue **b) Fixation / Pulsating Stimulus**



The Motor task consists of three conditions: left hand tapping (32 volumes), right hand tapping (32 volumes), and rest (71 volumes). The task is separated into three trials, each with 166 dynamics (343.9 seconds); the entire test takes 971.7 seconds to complete.

2.8 Functional Connectivity Analysis

2.8.1 MRI Image Preprocessing

Each of the participant's fMRI images was preprocessed using FSL (FMRIB's Software Library). Excess unwanted brain structures in high resolution T1 images were removed via BET; rigid body motion correction was completed using MCFLIRT; spatial smoothing was carried out using FWHM 6.0 mm; temporal filtering was applied with high pass frequency cut-off of 120 seconds. In addition, a low pass temporal filtering was also included to ensure the fMRI signal to fluctuate between $0.008<f<0.080$ Hz, the ideal bandwidth to examine functional connectivity of the DMN. Furthermore, the application of a low pass filter eliminates high frequency signals that can potentially confound the results. Participant's low-resolution functional data was registered to personal high resolution T1 anatomical image, which is consequently registered to a standardized 152 T1 MNI space.

2.8.2 Functional connectivity seeding analysis

Whole brain analysis of four relevant cognitive neural networks was completed (front-executive, FP, Mot, and DMN). The selection of seeds from these brain systems were derived based on literature that served as prominent hubs within each of the networks. The initial seeds (Table 2) were: posterior cingulate cortex (8, -56, 30; DMN), right anterior lateral prefrontal cortex (32, 40, 28; FE), right inferior parietal sulcus (26, -62, 52; FP), and right/left precentral gyrus (-36, 6, 26; Mot). Time-series data were extracted from these seeds with spherical regions of interest drawn around their respective MNI coordinates. Because the time-series data contained mixed information

from finger tapping left, finger tapping right, and rest task conditions, for the ease of analysis, this data required to be separated. To accomplish this, the time-series data were spliced based on the task condition (with the on/off timing of the condition), then concatenated to produce a homogeneous run of the same condition (e.g. if volumes 1-3, 8-10, 9-11 were left tapping, they were spliced out and merged to create a single file with all left tapping). To ensure the quality of data, the first three volumes were discarded to allow signal stabilization.

Subsequently, this data is cross-correlated with every voxel within the brain to establish functional connectivity maps of the neural networks. Individual-level within-subject results were generated by congregating the voxel-wise functional connectivity from different condition (left, right, and rest) via ordinary least square (OSL) in FSL. Similarly, for group results, a mixed-level OSL analysis was conducted. Specifically, at the mixed-effects level, the FSL program adopts FMRIB's Local Analysis of Mixed Effects (FLAME) that uses complex modelling methods for estimating the between-subject random-effects component of the mixed-effects variance – the sum of fixed-effects variance and random-effects variance (Figure 4).

In order to improve the normality of the data, Pearson's correlation coefficients (between the time-series of the initial seed region and other voxels in the brain) computed in MATLAB was converted into Fisher's z correlation via Fisher's r-to-z transformation. Fisher's transformation is applied to provide normal distribution for the correlation coefficients of fallers and non-fallers. This transformation makes the sample distribution normally distributed and makes the variance of the correlation coefficient constant for all values in the sample population correlation.

With the transformed correlation coefficient for each pair of ROI identified, I averaged all the ROI-pairs within each network to create a mean correlation coefficient to represent the corresponding network. For example, the Fisher's transformation output 15 sets of z-correlation coefficients (one for PCC-FMC, one for PCC-RMTG, one for PCC-RPHG, etc.) for the DMN, and then I averaged the 15 correlations into a single "mean DMN correlation". This is required to simplify statistical testing using Statistical Package for the Social Sciences (SPSS) program.

IBM SPSS Statistic 19 for windows was used to statistically test for significant group differences in between-network and within-network correlations. A one-way ANOVA was conducted with functional comorbidity index and average ABC scale score as covariates. The average ABC scale was included as a covariate variable as literature suggests falls-related self-perceived ability is associated with brain health [137, 138]. In a recent study, Davis and colleagues [137] demonstrated falls-related self-perceived capability is independently associated with brain volume, highlighting the importance of self-efficacy in maintaining proper balance, mobility, as well as cognitive functions. In accordance with this finding, Seeman and colleagues [138] found self-efficacy was associated with performances on verbal memory. Particularly, men with stronger self-efficacy beliefs were able to retain better verbal memory function over the period of 18 months [138]. In a sub-analysis using the same dataset, Seeman and colleagues [139] found weak self-efficacy is associated with increased risk of functional disabilities regardless of health status. These results support the Bandura's Social Cognitive Theory [140]. According to this theory, self-efficacy is a better predictor of performance than the actual physical capabilities [140]. The functional comorbidity index is an

estimate of the association of an individual's comorbidity and physical function [133], therefore it is also considered as a potential confounder.

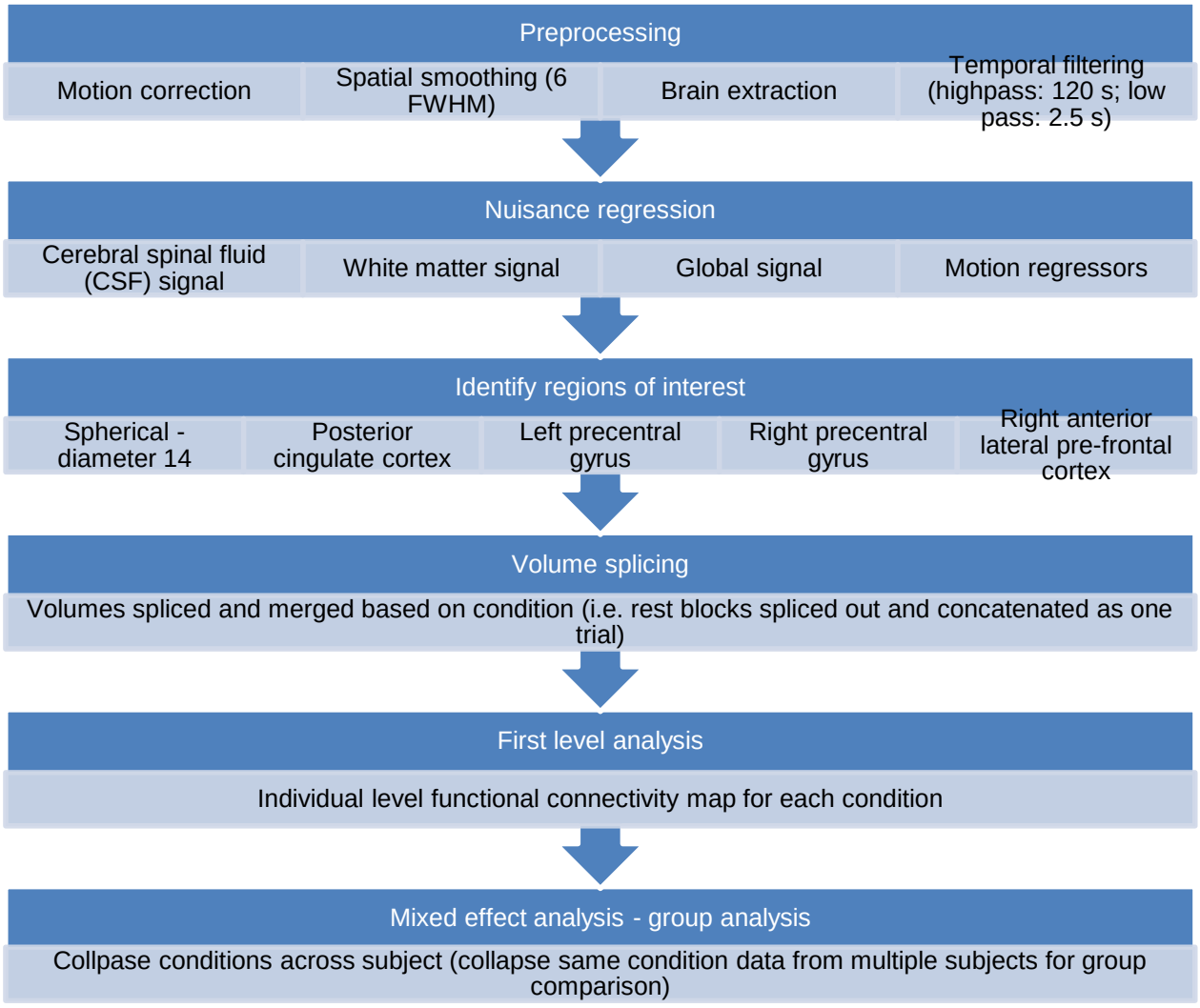
Table 2. Regions of Interest Within Each Functional Network

DMN	FE	FP	Mot
PCC*	RALPFC*	RIPS*	LPCG/RPCG*
FMC	RINS	RVV	LCB/RCB
RMTG	RPFC	RSMG	LPM/RPM
RPHG	RIFG	RSLOC	SMA
LMFG	RCING	RFEF	
RLOC			

*denote the initial seeds selected for the seeding analysis

PCC = posterior cingulate cortex; FMC = frontal medial cortex; RMTG = right middle temporal gyrus; RPHG = right parahippocampal gyrus; LMFG = left middle frontal gyrus; RLOC = right lateral parietal cortex; RALPFC = right anterior lateral prefrontal cortex; RINS = right insular sulcus; RPFC = right prefrontal cortex; RIFG = right inferior frontal gyrus; RCING = right cingulate; RIPS = right inferior parietal sulcus; RVV = right ventral visual; RSMG = right supramarginal gyrus; RSLOC = right lateral occipital cortex; RFEF = right frontal eye field; LPCG = left precentral gyrus; RPCG = right precentral gyrus; LCB = left cerebellum; RCB = right cerebellum; LPM = left premotor; RPM = right premotor; SMA = supplementary motor area

Figure 4. Breakdown of Functional Connectivity Analysis



2.9 Results

2.9.1 Demographic Variables and Cognitive Assessments

A total of 44 participants were recruited and completed this study. Table 3 summarizes the study descriptive statistics and cognitive performances of the cohort. Fallers (mean age =75.00) report an average of 3.30 falls and non-fallers (mean age =75.10) report an average of 0.29 falls 12 months prior to the study. The mean MMSE scores for fallers and non-fallers were 28.20 and 28.21 respectively while there was only a 0.50 difference in MoCA performance between fallers (24.50) and non-fallers (25.00). Other than history of falls, there were no significant differences between the two groups in all clinical measures. This indicates that standard clinical measures of cognitive and physical function do not differentiate these two groups of older adults.

Table 3. Study Demographics

a) With All Participants (35 females; 9 males)

Variable*	Non-Fallers (n=23) Mean (SD)	Fallers (n=21) Mean (SD)	p-value
Age	75.00 (3.15)	75.10 (3.33)	0.919
Falls	0.29 (0.46)	3.30 (3.99)	**0.001**
MoCA	25.00 (3.35)	24.50 (2.89)	0.603
MMSE	28.21 (1.38)	28.20 (1.64)	0.985
FCI	2.79 (1.93)	3.10 (1.80)	0.590
GDS	0.39 (0.78)	0.57 (1.03)	0.515
ABC	87.20 (10.25)	79.30 (21.75)	0.121
TUG	7.31 (1.09)	8.66 (4.13)	0.131
PPA	0.15 (0.81)	0.60 (0.87)	0.084
Stroop	54.55 (24.09)	48.84 (31.01)	0.489
Trails	44.00 (39.41)	83.63 (171.83)	0.243
Digits	4.35 (2.08)	2.95 (2.04)	0.054

b) With Outlier Removed (34 females; 9 males)

Variable*	Non-Fallers (n=23) Mean (SD)	Fallers (n=20) Mean (SD)	p-value
Age	75.00 (3.15)	74.95 (3.36)	0.958
Falls	0.29 (0.46)	3.37 (4.09)	**0.001**
MoCA	25.00 (3.35)	24.47 (2.97)	0.594
MMSE	28.21 (1.38)	28.11 (1.63)	0.824
FCI	2.79 (1.93)	3.05 (1.84)	0.656
GDS	0.39 (0.78)	0.50 (1.00)	0.692
ABC	87.20 (10.25)	82.85 (15.27)	0.271
TUG	7.31 (1.09)	8.50 (4.17)	0.188
PPA	0.15 (0.81)	0.52 (0.83)	0.141
Stroop	54.55 (24.09)	44.39 (26.20)	0.192
Trails	44.00 (39.41)	48.26 (37.42)	0.662
Digits	4.35 (2.08)	3.21 (1.90)	0.100

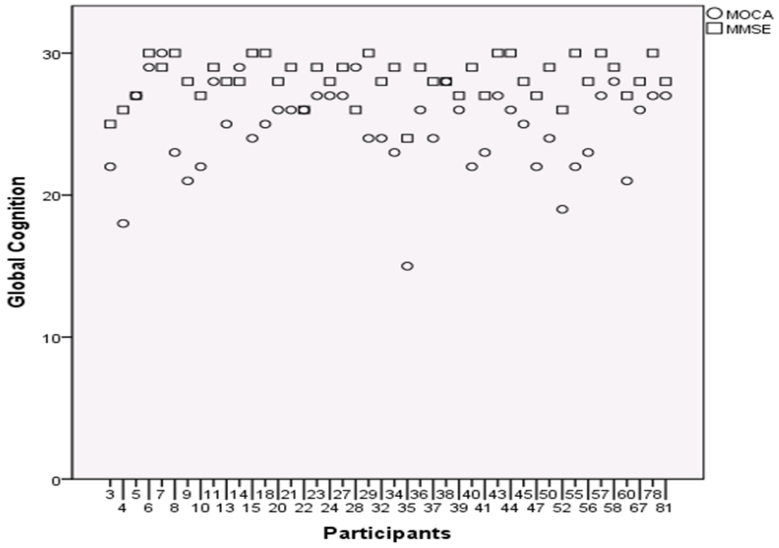
* MoCA=Montreal Cognitive Assessment; MMSE=Mini-Mental State Examination test; FCI=Functional Comorbidity Index; GDS=Geriatric Depression Scale; ABC=Activities-specific Balance Confidence scale;TUG=Time-Up-and-Go test; PPA=Physiological Profile Assessment

Stroop is calculated by Stroop3-Stroop2; Trails is calculated by Trail Making B-A; Digits is calculated by Digits Backward-Forward

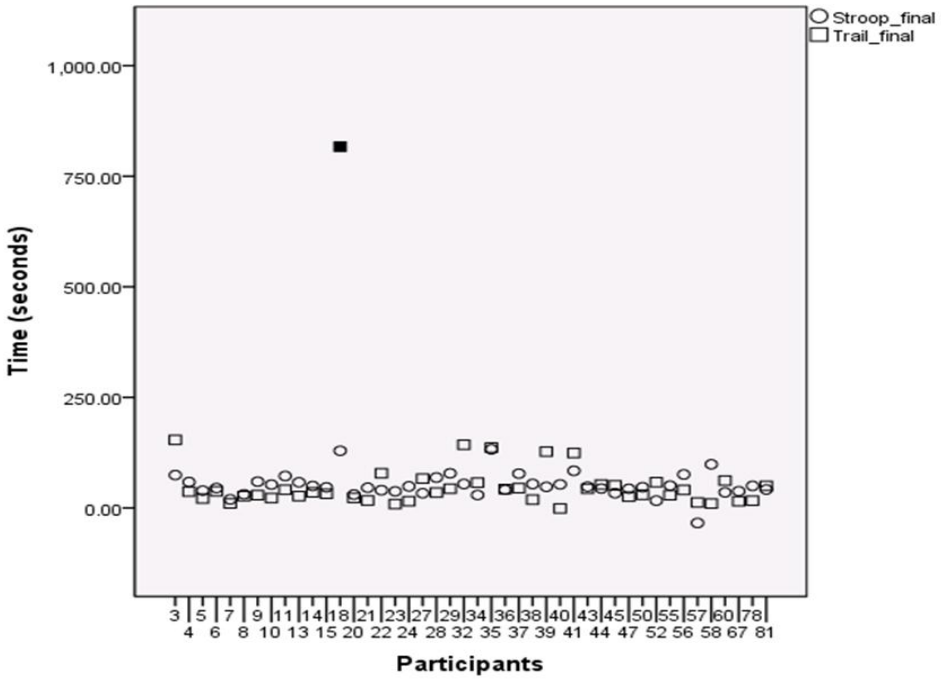
Outliers are defined as scores 3 SD above or below the group mean (Figure 5)

Figure 5. Study Scatterplot

a) Global Cognition of Study Participants

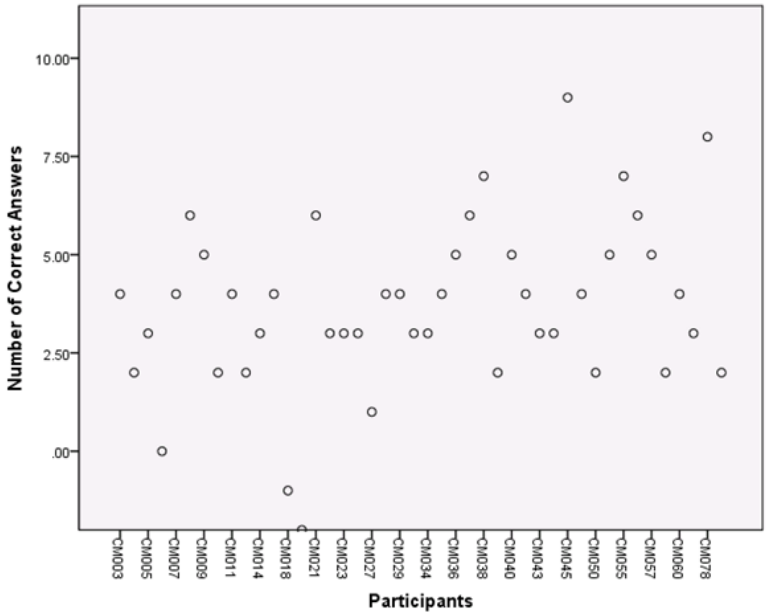


b) Participant Performance on the Stroop Test and Trail Making Test



*Solid filled square indicates the outlier on the Trail Making test

c) Participant Performance on the Digit Forward and Backward Test



2.9.2 Group Differences in Functional Connectivity

Results of comparing the within network differences of fallers and non-fallers are shown in Table 4, and statistically, no significant differences can be found within each of the four networks identified in the study. However, a general trend can be observed. Specifically, non-fallers showed an overall greater correlation coefficient within several networks: the DMN (in rest and right conditions), the FP network (in all three conditions), the left side Mot network (in all three conditions), and the right side Mot network (in rest and left conditions).

Table 4. Within-Network Mean Fisher's z Transformed Correlation Coefficient Between Groups

	Non-Fallers (n=23)		Fallers (n=21)		
Variable*	Mean	SD	Mean	SD	p-value
DMN rest	0.2405	0.1686	0.2184	0.1418	0.5910
DMN right	0.2950	0.1621	0.2422	0.1656	0.3206
DMN left	0.2470	0.2047	0.2576	0.1583	0.9050
FE rest	0.1863	0.1110	0.2027	0.0957	0.5621
FE right	0.1467	0.1296	0.1657	0.0657	0.4804
FE left	0.1614	0.1587	0.1545	0.1101	0.9483
FP rest	0.3151	0.1728	0.2778	0.1361	0.3036
FP right	0.3498	0.2158	0.2825	0.1921	0.1376
FP left	0.3297	0.2164	0.3061	0.1649	0.4629
Left Mot rest	0.2768	0.1864	0.2294	0.1666	0.3756
Left Mot right	0.2875	0.1410	0.2209	0.2076	0.1514
Left Mot left	0.2545	0.1949	0.2153	0.2141	0.4078
Right Mot rest	0.2327	0.1704	0.1964	0.1537	0.4232
Right Mot right	0.2058	0.1691	0.2125	0.2231	0.8867
Right Mot left	0.2688	0.1901	0.1980	0.1787	0.1096

*DMN = DMN; FE = fronto-executive network; FP = fronto-parietal network; Mot = motor network

Table 5 illustrates the mean fisher's Z transformed correlation coefficient differences across networks between fallers and non-fallers, and interestingly, the FP network appears to be the most relevant network as it displays most significant differences between fallers and non-fallers. Specifically, we found fallers show greater correlation in the DMN-FP (right condition, p=0.040), and less correlation in the right side Mot-FP (rest condition, p=0.048), the right side Mot-FP (left condition, p=0.016), and left side Mot-FP (rest condition, p=0.025). Figure 6 graphically present the same data.

Table 5. Between-Network Mean Fisher's z Transformed Correlation Coefficient Between Groups

Variable*	Non-Fallers (n=23)		Fallers (n=21)		
	Mean	SD	Mean	SD	p-value
DMN-FE rest	-0.0195	0.0809	-0.0201	0.0782	0.8822
DMN-FE right	-0.0264	0.0845	-0.0369	0.1071	0.3620
DMN-FE left	-0.0451	0.0926	-0.0400	0.1106	0.7248
DMN-FP rest	-0.1812	0.1447	-0.1462	0.1103	0.3725
DMN-FP right*	-0.2358	0.1788	-0.1360	0.1380	**0.0404**
DMN-FP left	-0.1820	0.1397	-0.1598	0.1323	0.6242
FE-FP rest	-0.0060	0.0972	-0.0153	0.0780	0.8424
FE-FP right	-0.0039	0.1427	-0.0005	0.1079	0.7495
FE-FP left	0.0081	0.1008	-0.0110	0.0952	0.5775
Right Mot-DMN rest	-0.1658	0.1330	-0.1498	0.1194	0.7613
Right Mot-DMN right	-0.1641	0.1271	-0.1390	0.1297	0.4737
Right Mot-DMN left	-0.1817	0.1271	-0.1602	0.1122	0.5300
Right Mot-FE rest	-0.0030	0.0844	0.0182	0.0936	0.2941
Right Mot-FE right	-0.0290	0.1492	0.0209	0.1053	0.2282
Right Mot-FE left	-0.0044	0.1282	0.0091	0.0842	0.8742
Right Mot-FP rest*	0.2339	0.0973	0.1793	0.1057	**0.0480**
Right Mot-FP right	0.2452	0.1246	0.1710	0.1537	0.0644
Right Mot-FP left*	0.2647	0.1556	0.1847	0.1152	**0.0159**
Left Mot-DMN rest	-0.1711	0.1405	-0.1357	0.0970	0.3960
Left Mot-DMN right	-0.1819	0.1345	-0.1395	0.1015	0.1828
Left Mot-DMN left	-0.1625	0.1308	-0.1777	0.1056	0.6929
Left Mot-FE rest	0.0192	0.0842	0.0155	0.0900	0.9679
Left Mot-FE right	0.0123	0.1480	0.0367	0.0977	0.5199
Left Mot-FE left	0.0493	0.0875	0.0035	0.1074	0.1333
Left Mot-FP rest*	0.2201	0.1157	0.1539	0.0852	**0.0248**
Left Mot-FP right	0.2325	0.1441	0.1656	0.1267	0.0900
Left Mot-FP left	0.2218	0.1734	0.1825	0.1046	0.2351

*DMN = DMN; FE = fronto-executive network; FP = fronto-parietal network; Mot = motor network; rest = rest condition; right = right finger tapping condition; left = left finger tapping condition

Figure 6. Between-Network Functional Connectivity Group Difference

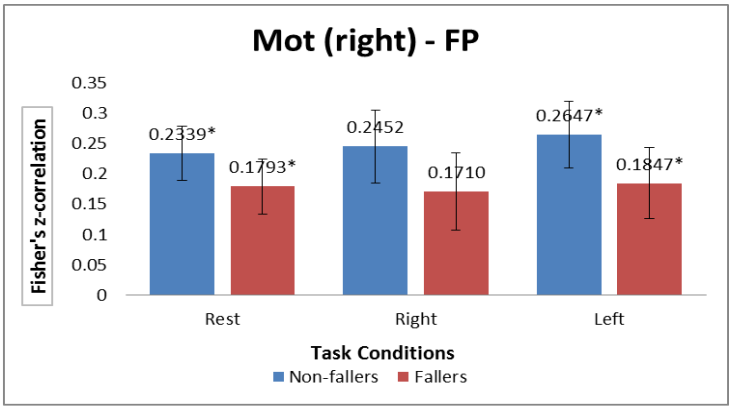


Figure 6. a) Right Motor Network vs. Fronto-Parietal Network Correlations

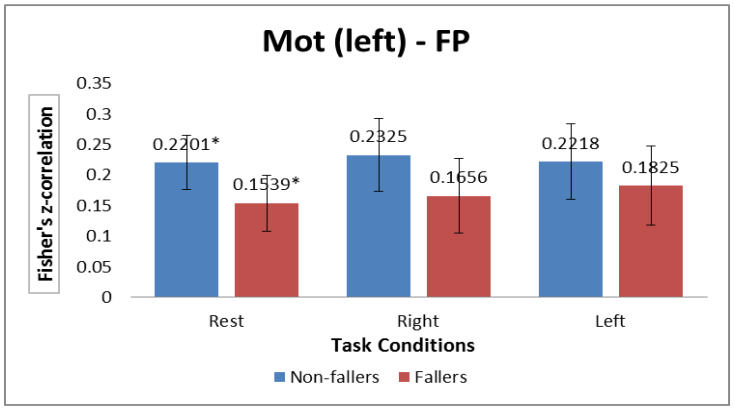


Figure 6. b) Left Motor Network vs. Fronto-Parietal Network Correlations

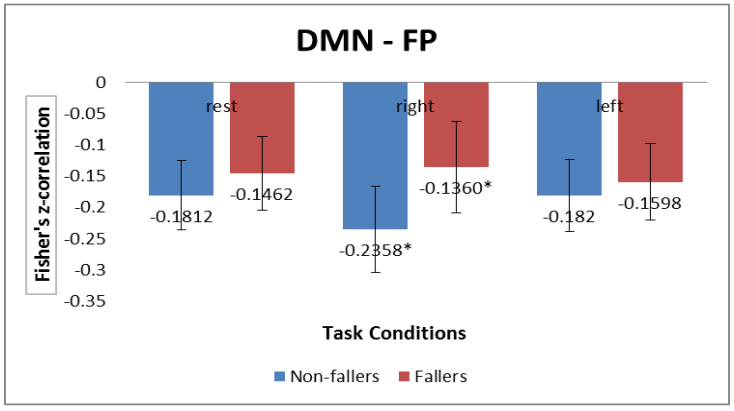


Figure 6. c) Default Mode Network vs. Fronto-Parietal Network Correlations

*denotes significant between-group differences in fisher's z correlation coefficient at $p<0.05$; rest = rest condition; right = right condition; left = left condition

Error bars represent 95% confidence interval

2.10 Discussion

The primary aim of this thesis was to explore the differences in functional connectivity between fallers and non-fallers, and indeed, significant differences were found between neural networks. Specifically, fallers show a decreased connectivity between Mot network and FP network, as well as an increased connectivity between the DMN and FP network. To my knowledge, this provides novel evidence that demonstrated the existence of a distinct relationship between falls and changes in neural network patterns in community dwelling older adults.

Falls among seniors have been examined extensively in the literature and studies have based their research on the association between falls and cognition [2, 16, 23]. Impaired global cognitive function has been identified as a risk factor for falls [2], and standard neuropsychological test such as the MMSE and the MoCA are generally used to assess global cognitive and broadly classify individuals as normal, mild cognitively impaired, or with dementia [26]. Other studies have focused on specific domains of cognitive function, particularly executive functions and its relationship with falls and falls risk [29, 39].

The MMSE is a questionnaire designed as a clinical tool to assess for cognitive impairment and is found to be associated with dementia [141]. In a prospective cohort study, the MMSE is found to be predictive of falls prospectively over eight year period [23].

The MoCA is 30-point test that covers short-term memory, visuospatial abilities, aspects of executive functions, attention, language abilities, and orientation [26]. It is reported to

detect mild cognitive impairment, a key predictor of falls [2], with high sensitivity and specificity [26].

The Stroop Test, Trail Making B Test, and Digit Symbol Substitution Test are standardized neuropsychological tests administered to assess response inhibition, set-shifting and processing speed domains of executive functions respectively. Studies report declined function of these executive functions domains result in increased falls risk in older adults [28, 39, 46, 47, 54].

Despite the listed research presenting strong evidence on the association of cognitive function and falls or falls risk, the basis of these studies relied on notable l differences between fallers and non-fallers as assessed by the standard clinical neuropsychological tests. The possibility of non-detectable changes in the underlying neural network is an important aspect that has not been discussed by the previous research, because early detection allows for early implementation of intervention or treatment.

Considering the evidence discussed above, it is surprising that the participants performed similarly on the standardized physical and neuropsychological tests regardless of their group identification. Specifically, no significant differences were found in the FCI, the average ABC scale, the TUG test, the PPA, the Stroop Test, the Trail Making Test, and the Digits Forward and Backward Test (Table 3). Thus, this is indicative that limitations exist with these clinical tests in identifying early neural network changes. Interestingly, falls history was the only measure in my thesis that was able to identify these changes.

The DMN has been studied extensively primarily due to its clinical relevance to pathologies such as Alzheimer's disease [142, 143] and schizophrenia [144]. Functionally, the DMN had been shown to be involved in aspects of executive functions including working memory [145] as well as age related cognitive abilities such as spatial memory, and task switching [146]. It is widely recognized as a network that exhibits high levels of activity while at rest, but deactivates during cognitively demanding task-oriented processes [146, 147]. Specifically, one study suggested the existence of a strong negative correlation between the DMN and "task-positive" neural systems in younger adults [148]. In a follow up sub-analysis study, Fox and colleagues [106] confirmed the presence of this anti-correlation between task-positive and task-negative networks indeed originated from a biological basis, as opposed to studies that claim this negative relationship can be the by-product of global signal regression [149-151]. Similarly, in a cross-sectional study utilizing seed-voxel based analysis, Wu and colleagues [152] report older adults showed reduced negative correlation (hence more positive correlation) between the DMN and regions in the frontal cortex, and inferior precentral sulcus. Uddin and colleagues [147] consolidated the existence of this anti-correlation by demonstrating, in younger adults, the posterior cingulate cortex (PCC – key node in the DMN) is negatively associated with extrastriate visual areas, parietal network, anterior cingulate, medial frontal gyrus, lateral prefrontal, lateral temporal networks, and precuneus.

The FP network is involved in both top-down cognitive and bottom-up sensory control of visual-attention [153]. In a recent functional MRI study, Madden and colleagues report increased frontoparietal activity is observed in normal aging. The authors associated

this increased activity with improved performance on a visual searching task administered to assess participant's top-down cognitive visual attention control. This relationship is explained as a compensatory action for reduced bottom-up sensory control in the older adults [154]. This result is in accord with a recent functional MRI study investigating differences in brain activity between older and younger adults during a visuomotor task [155]. The authors found more extensive activation of the FP network in the older adults and discussed this age-related difference in brain activity as a consequence of older adult's increased effort to focus on task and inhibit task-unrelated information (i.e. processing visual and somatosensory information). Again, older adults require increased neural resources to compensate for declined function.

My results replicate and extend previous findings reporting a negative relationship between DMN and FP network [156, 157] in community dwelling older adults. The FP network, as described by Corbetta and colleagues [158], controls both stimulus-related attention and goal-oriented attention, therefore is considered to be a "task-positive" network. Task-positive network refers to networks that are activated or remains in activity with the presence of an external stimuli. Fransson and colleagues [156] explained the inverse relationship between the DMN and the FP network, a task-positive network, is reflective of a separation of introspective oriented (self-referential mental activities, processes, or thoughts) vs. extrospective attention (involved in readiness to react to external stimuli in the environment), and this anticorrelation represented the dichotomy between brain regions of increased activity for task performance and decreased activity for brain regions unrelated to the task at hand. In other words, the DMN and FP network are suppressed in an alternating fashion

depending on the task condition. My results show (Figure 2) the non-fallers display a significantly greater negative correlation than the fallers, suggesting the non-fallers were more capable in suppressing the DMN while engaged in task, thus resembling the neural capacity similar to younger adults [106, 147]. Consequently, this is indicative that falls in older adults is a signal of neural connectivity alterations, in addition to the potential health related problems.

One study suggests the FP network, in addition to attentional control, also participates in motor preparation, particularly in the executive phase of neural processes of motor decision and motor-planning [159]. Specifically, the posterior parietal cortex receives visual sensory inputs from primary visual cortex and, in conjunction with supplementary motor area, processes and conveys this information into appropriate motor outputs [160]. Fogassi and colleagues [161] proposed the inferior parietal lobule contains regions responsible for motor movement control, and neurons of the rostral inferior parietal lobule actively govern the execution of goal-oriented movements. This evidence is supported by results reported by Cui and colleagues [162]. Specifically, they explained the posterior parietal cortex plays an important role in conveying sensorimotor information to movement, including both movement planning and movement decision [162].

The Mot network is involved in a higher level top-down cognitive control of movement that includes motor-planning, initiation, execution, and coordination [163-165]. Literature suggests motor function impairments with aging can be attributed to reduction in both gray matter and white matter volume [166-168], which potentially can lead to disrupted network connectivity. Critically, studies have showed older adults required recruitment

of additional brain regions relative to younger adults during motor task performance [169, 170]. This over activation of the aged brain was explained by Cabeza and colleagues [171] as the compensatory brain activity that is positively correlated with performance.

Results from my analysis show the non-fallers exhibit higher functional connectivity between the Mot and FP networks. As the evidence suggests, this can be explained by the non-faller's ability to efficiently recruit FP network in supporting motor functions, and/or the ability to continue receive higher order cognitive motor inputs from the FP network by maintaining a healthy connection between the two networks. Similar to how fallers show reduced connectivity between the Mot and FP networks, Inman and colleagues [172] found diminished connectivity in the two networks in stroke survivors, suggesting the fallers display a network connectivity relationship resembling stroke patients. These results illustrate falls may be a product of reduced motor preparatory inputs from FP network.

Initially, I proposed there should be significant differences within the key neural networks between fallers and non-fallers. The rationale behind such hypothesis arises from evidence in the current literature. Specifically, studies report age-related disruptions within these specific networks [103, 107], and in an intervention study, Voss and colleagues [118] distinctively showed older adults displayed reduced connectivity within the DMN, FP network and between some of the regions within the Mot network. Through exercise intervention, they demonstrated an increased in connectivity, or restoration of age-related deterioration, in the DMN, FE network, and FP network [118].

With this evidence, I rationalized non-fallers, with neural network patterns resembling younger adults [147], should exhibit significantly increased connectivity within the neural networks discussed; however, no significant differences were found within the neural systems.

In summary, there are significant differences in functional connectivity between fallers and non-fallers. Specifically, the non-fallers' network connectivity patterns between neural systems appear to correspond to a younger, healthier neural network [106, 147]. In contrast, the neural connectivity of fallers is more disrupted (between FP and Mot) and less differentiated (between DMN and FP), thus their network organization is more similar to patients with dementia or at more advanced stages of aging [156, 172]. These results provide support for the role of higher order cognitive motor functions in falls among older adults and offer evidence that falls can be an early indicator of subtle changes (undetectable by standard neuropsychological tests) in the neural systems. Furthermore, given that the no other observable significant clinical difference can be found between fallers and non-fallers except their history of falls, it is logical and likely falls itself can be a precursor or early sign for cognitive changes among older adults. Also, the inability to find any differences within each of the four neural networks suggest that changes in the between network functional connectivity may be a good early indicator for future falls.

3. CONCLUSION AND LIMITATIONS

Falls among senior is and will continue to be a prominent issue globally as the number of older adults is increasing at a rapid rate. In order to remedy this problem, researchers in the field of falls prevention have closely examined falls and gained extensive knowledge regarding various cognitive and physical factors contributing to elevated risks of falling in seniors. With advances in medical imaging technology and techniques, researchers now have the opportunity to study falls with alternative methods that provides new insights to the field of falls prevention. Particularly, there is a growing interest in functional connectivity and resting state analysis. Functional connectivity is a method of correlating neurophysiological events based on synchronous fluctuating neural activities of different brain networks, and is found to show high sensitivity in identifying neuropsychiatric conditions as well as examining network integrity. Therefore, functional connectivity analysis serves as a powerful tool to study the effects of aging on brain systems. For the purpose of the thesis, I applied functional connectivity analysis, a novel aspect to the field of falls prevention, to inspect and understand the underlying difference in neural systems between fallers and non-fallers.

I initially hypothesized to find inter-network and intra-network connectivity differences between fallers and non-fallers. Specifically, I expected to find reduced within-system correlations for the fallers in the DMN, FE network, FP network and the Mot network. For between-system connectivity, I expected to find increased correlation for the fallers between the DMN and both FE and FP networks. Indeed, the results from analysis showed fallers exhibit a significant increased correlation between the DMN and fronto-parietal network. Conversely, fallers displayed a reduced connectivity between the Mot

network and the FP network. However, I did not observe significant differences between group in the within-network or between-network (other than the previously noted networks) as I originally hypothesized. These results conform to the current evidence on functional integrity of neural networks of the aging brain, and support the view that falls may be a precursor to clinical detectable cognitive changes. Clinicians and future researchers may apply these findings to develop alternative intervention or prevention strategies targeting underlying neural basis for falls, as opposed to the present approach that primary focus on physical risk factors.

There are key limitations to this research thesis: 1) MRI scanning may be stressful and physically draining for seniors. Therefore, the study requirements may bias toward the inclusion of healthier seniors (i.e. selection bias). 2) The result from the study is limited by the study design, as cross-sectional studies do not infer casual relationships. The study results (i.e. differences in functional connectivity) may be due to the effect of the event/condition (i.e. fall) rather than as a cause. To put this in the context of this study, falls may be argued to be the cause for variations in brain function and not the direct result of the differences in the brain. 3) Because falls are self-reported by the individual, and falls recall among seniors can be unreliable, misclassifying a participant (i.e. misclassification bias) is possible. 4) White matter lesion had not been accounted for within the scope of the thesis. White matter lesion is reported to negatively impact cognitive function [6, 66] and gait performances [61, 173]. Changes to the white matter integrity can potentially be associated with the differences in functional connectivity observed. 5) Multiple comparisons with ANOVA can lead to increased probability of

committing type-one error. However, the study is only meant to provide an exploratory view of the problem.

To reconcile for the limitations and extend the findings of this thesis research, future research should develop a longitudinal study examining the effect of physical exercise, a widely accepted intervention to improve cognition, on changes in the key inter-network functional connections that are different between fallers and non-fallers.

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